8 Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-Saharan Africa. *BMJ Glob Health* 2018; **3:** e000347.
9 Williams P, Isaacs D, Berkley JA. Antimicrobial resistance among children in sub-Saharan Africa. *Lancet Infect Dis* 2018; **18:** e33–44.
10 Leopold SJ, van Leth F, Tarekegn H, Schultsz C. Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review. *J Antimicrob Chemother* 2014; **69:** 2337–53.

Early vaccination: a provisional measure to prevent measles in infants

The optimal age for measles-containing vaccine (MCV) administration depends on various factors, mainly the duration of the protection induced by transplacentally acquired maternal immunity, the maturity of the infant's immune system, and the average age of measles infection in different geographical areas.[1] Demographics and vaccine coverage also contribute.[2]

Initially, experts thought that if an area had a high risk of measles outbreaks, a first dose of MCV at 9 months of age could be enough to protect most infants, as those younger than 9 months could avoid infection through transplacentally acquired immunity. Subsequently, it was shown that this supposition was partly wrong, as many measles cases, sometimes very severe, were diagnosed in infants younger than 6 months.[3] This finding was attributed to a shorter-than-expected duration (9–12 months) of passive maternal immunity, evidenced in both infants born from immunised mothers and those born from mothers with naturally acquired immunity. It was shown that vaccination stimulated the immune system less than natural infection, and infants born from vaccinated mothers had lower specific antibody titres with more rapidly waning protection than infants born from naturally infected mothers.[4] Nevertheless, with the introduction of MCV administration, the circulation of measles virus progressively declined and, without this natural booster, even previously naturally infected mothers transferred reduced antibody concentrations to their fetuses.[5]

To address the problem of measles infection in young infants, an early MCV dose before 9 months of age was suggested. Infants living in or travelling to countries with frequent measles outbreaks, or considered at risk because of HIV exposure or infection, and refugees or people living in conflict zones were the target populations. However, because of the risk that an early MCV dose could lead to poor short-term and long-term protection, this dose was considered only supplemental. Infants vaccinated before 9 months of age had to receive the usual two doses at scheduled times to achieve long-term protection.[1]

Unfortunately, the real effect of an early MCV dose has not been definitively established. Attempts to fill this gap have been made by Laura Nic Lochlainn and colleagues with two systematic reviews and meta-analyses published in *The Lancet Infectious Diseases*.[6,7] The results indicate that MCV administration before 9 months of age is safe and immunogenic.[6] Moreover, early immunisation did not blunt the immune response to subsequent MCV doses.[7] Consequently, the authors concluded that administration of MCV to infants younger than 9 months can be an effective solution to reduce measles-related morbidity and mortality in a substantial proportion of infants at risk.

However, the results of Nic Lochlainn and colleagues strongly suggest that MCV administration before 9 months of age must only be considered as an emergency solution to contain or prevent outbreaks and cannot replace either scheduled dose. Compared with infants administered MCV at 9 months of age or later, seroconversion and antibody concentrations in those vaccinated before 9 months of age were significantly reduced. Vaccine efficacy was 51% versus 83%, highlighting that a substantial proportion of infants younger than 9 months remained susceptible to measles, and that only further doses could ensure that all infants were protected. Moreover, analysis of the immunogenicity and efficacy of further doses, despite showing that MCV efficacy and cell-mediated responses to a second and a third dose were independent of the age of the first dose, suggests that an early dose might decrease long-term protection because further doses were associated with reduced antibody titres and avidity. Further studies are needed to solve the problem of reduced long-term immunity after early MCV administration. In the meantime,


Voisin/Phanie/Science Photo Library

Published **Online** September 20, 2019 https://doi.org/10.1016/S1473-3099(19)30520-1

See **Articles** pages 1235 and 1246

WHO's recommendations on vaccination must be followed.

The need for a three-dose regimen presents organisational and economic difficulties, particularly in low-income countries. Only countries with well established immunisation programmes can rely on routine services to deliver the second and third doses. Together with additional expenses, which are difficult to sustain in low-income countries, the uptake of routine vaccination after receipt of an early dose can be suboptimal. Although data on vaccination uptake in developing countries are insufficient, a Canadian study showed that approximately 20% of early-vaccinated children, mainly in low-income families, did not receive further doses at the appropriate time.[8]

The most important obstacle to measles elimination by 2020 in five of the six WHO-targeted regions is the poor vaccination coverage in countries where measles had been nearly eradicated. Coverage with two doses at recommended ages was less than 95% in 96·5% of European countries, and the prevalence of measles protection according to antibody titres was significantly lower than the herd immunity threshold in these countries (76% *vs* 95%).[9] Similar suboptimal vaccination coverage was seen in several other countries outside Europe, including the USA.[10] Circulation of measles virus among adolescents and adults predominantly affects unvaccinated young infants. Only total compliance to recommendations can solve the problem of poor vaccination coverage.

*Nicola Principi, Susanna Esposito
Università degli Studi di Milano, 20122 Milan, Italy (NP); and Pietro Barilla Children's Hospital, Department of Medicine and Surgery, University of Parma, Parma, Italy (SE)
nicola.principi@unimi.it

We declare no competing interests.

1 WHO. Measles vaccines: WHO position paper–April 2017. *Wkly Epidemiol Rec* 2017; **92:** 205–27.
2 McKee A, Ferrari MJ, Shea K. Correlation between measles vaccine doses: implications for the maintenance of elimination. *Epidemiol Infect* 2018; **146:** 468–75.
3 European Centre for Disease Prevention and Control. Surveillance report: measles and rubella surveillance 2017. 2018. https://ecdc.europa.eu/sites/portal/files/documents/Measles-and-Rubella-Surveillance-2017.pdf (accessed Aug 19, 2019).
4 Brugha R, Ramsay M, Forsey T, Brown D. A study of maternally derived measles antibody in infants born to naturally infected and vaccinated women. *Epidemiol Infect* 1996; **117:** 519–24.
5 Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ* 2010; **340:** c1626.
6 Nic Lochlainn LM, de Gier B, van der Maas N, et al. Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; published online Sept 20. https://doi.org/10.1016/S1473-3099(19)30395-0.
7 Nic Lochlainn LM, de Gier B, van der Maas N, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; published online Sept 20. https://doi.org/10.1016/S1473-3099(19)30396-2.
8 Guo X, Simmonds KA, Svenson J, MacDonald SE. Do children who receive an 'early dose' of MMR vaccine during a measles outbreak return for their regularly scheduled dose? A retrospective population-based study. *BMJ Open* 2016; **6:** e012803.
9 Plans-Rubió P. Low percentages of measles vaccination coverage with two doses of vaccine and low herd immunity levels explain measles incidence and persistence of measles in the European Union in 2017–2018. *Eur J Clin Microbiol Infect Dis* 2019; **38:** 1719–29.
10 Centers for Disease Control and Prevention. Measles cases and outbreaks. 2018. https://www.cdc.gov/measles/cases-outbreaks.html (accessed Aug 19, 2019).

HCV, injection drug use, and the importance of harm reduction in Kenya

Published Online September 17, 2019 https://doi.org/10.1016/S1473-3099(19)30407-4

See Articles page 1255

Matthew Akiyama and colleagues' study[1] in *The Lancet Infectious Diseases* fills an important gap in our understanding of hepatitis C virus (HCV) prevalence and risk factors among a geographically diverse sample of people who inject drugs (PWID) in Kenya and, by extension, other parts of sub-Saharan Africa and similar settings. The authors also reiterate the importance of supporting a robust array of harm-reduction services for PWID to prevent excess morbidity and mortality associated with infectious diseases. These services are especially relevant during nascent epidemics, as appears to be the case with HCV transmission among PWID in Kenya, where there is opportunity for primary prevention of infectious disease transmission. Government investment in harm reduction and provision of safe injecting supplies is rare worldwide, although typically successful when comprehensively established.[2] Therefore, Kenya's programmes could be a model to inform harm-reduction programming in other nations in sub-Saharan Africa and beyond. Furthermore, as Akiyama and colleagues suggest,[1] targeted implementation based on geographical or